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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,618	02/06/2004	Thomas W. Dubensky JR.	ANZ-1200-UT	8471

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Biotechnology Law Group
c/o Portfolioip
P.O. Box 52050
Minneapolis, MN 55402

EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
10/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,618	DUBENSKY ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21,83-87,97-107-118,128-189* is/are pending in the application.

4a) Of the above claim(s) *108 and 139* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21,83-87,97-107,109-118,128-138 and 140-189* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/15/08&7/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/15/08 has been entered.

Claims 20, 21, 83-87, 97-107, 109-118, 128-138 and 140-149 and new claims 150-189, elected species uvrA and uvrB, are currently under examination. Claims 108 and 139 were previously withdrawn from consideration.

Claim Rejections - 35 USC § 112-2nd paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 20, 21, 83-87, 97-107, 109-118, 128-138, 140-149 and 150-189 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 152 are vague and confusing because it is unclear what is encompassed by 'a genetic mutation that attenuates the ability of the bacterium to repair its modified nucleic acid relative to wild type". It is unclear what structure, e.g., what mutation, would cause this modified activity. The metes and bounds of the

invention cannot be understood as the mutation is not readily ascertained from the description in the claim. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. The specific mutation is a critical limitation and must be included in the claim.

Claims 20 and 152 are also vague and confusing because they are drawn to a method of treating or preventing *any* disease in a host yet the claims reads on solely the use of a L.monocytogenes bacterium. It does not appear this bacterium could treat or prevent a disease other than one caused by L.monocytogenes. Clarification is requested.

Claims 21 and 158 are vague and confusing because it recites 'the antigen' but the claim does not make it clear whether or not this is a heterologous antigen, e.g., is the bacterium transformed with heterologous DNA or is this a homologous antigen being expressed. The claim also does not state that the baterium has been modified so that it may not repair its modified nucleic acid. It is unclear whether this is Applicant's intention. Clarification and/or correction is requested.

Claims 20 and 98, 152, 163, 175 and 180 refer to 'wild type'. This is vague and indefinite. The claims should be amended to recite 'wild type L.monocytogenes bacterium'.

Claim Rejections - 35 USC § 112-Scope of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 20, 21, 83-92, 95-107, 109-123, 127-138 and 140-149 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "methods of inducing an immune response to a heterologous antigen in a host comprising administering an effective amount of a vaccine comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene which has been attenuated by treatement with psoralen S-59 (4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen) and ultraviolet light irradiation wherein the mutant bacterium expresses the heterlologous antigen"; "methods of treating disease caused *by L.monocytogeneis* in a host comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene which has been attenuated by treatement with psoralen S-59 (4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen) and ultraviolet light irradiation" and "a method of inducing an immune response to a heterologous antigen in a host comprising administering ,an effective amount of a vaccine comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrABgene which has been attenuated by treatement with psoralen S-59 (4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen) and ultraviolet light irradiation wherein the mutant bacterium expresses the heterologous antigen" and does not reasonably provide enablement for "A method of preventing or treating a disease in a host, comprising administering to the

host an effective amount of the vaccine of claim 1 a vaccine comprising *any* modified bacterium microbe, wherein the nucleic acid of the microbe has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the microbe is attenuated for proliferation, relative to the bacterium prior to modification, and wherein the modified bacterium expresses the antigen" or "a method of inducing an immune response to an antigen comprising administering to the host an effective amount of a vaccine comprising a modified bacterium, wherein the nucleic acid of the microbe has been modified by reaction with a nucleic acid targeted compound that reacts directly with the nucleic acid so that the microbe is attenuated for proliferation, and wherein the microbe expresses the antigen." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to "A method of preventing or treating a disease in a host, comprising administering to the host an effective amount of the vaccine of claim 1 a vaccine comprising ***any*** modified bacterium, wherein the nucleic acid of the microbe has been modified by reaction with a *nucleic acid targeted compound* that reacts directly with the nucleic acid so that the microbe is attenuated for proliferation" or "a method of inducing an immune response to an antigen comprising administering to the host an effective amount of a vaccine comprising ***any*** free-living microbe, wherein the nucleic acid of the microbe has been modified by reaction with a

nucleic acid targeted compound that reacts directly with the nucleic acid so that the microbe is attenuated for proliferation, and wherein the microbe expresses the antigen."

These claims encompass an incredibly large number of bacterium with an incredibly large number of different modification possiblities. The use of any 'nucleic acid targeted compound' is also included which can attenuate proliferation by any means.

The instant specification has shown that microbial vaccines could be made exquisitely sensitive to killing by treatment with S-59 psoralen and UVA light. Mutant strains of Listeria monocytogenes were made unable to repair psoralen-DNA corsslinks by deleting the ultraviolet light resistance uvrAB genes which are required for nucleotide-excision repair. It was shown that Listeria monocytogenes uvrAB mutants were much more sensitive to S-59/UVA light inactivation as compared with the parental Listeria monocytogenes strain having intact DNA repair. These mutant, inactivated Listeria monocytogenes uvrAB mutants maintained their metabolic activity and were able to synthesize and create new protein. As a result, these Psoralen/UVA treated Listeria monocytogenes uvrAB mutants retained full ability to infect dendritic cells, escape from the phagolysosome and program presentation of antigen via the class I pathway. Examples 15 and 16 provide successful treatment results using the vaccines comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene which has been attenuated by treatement with psoralen S-59 and ultraviolet light.

In the present case, the applicant has neither provided any direction or guidance, nor any working examples in the specification as to any potential mutations of

genes from other microbes (viruses, parasites), other species of bacteria (other Listeria species) or other Genus of bacteria that would satisfy the limitations of the claims. The claims read on any mutation to the uvrA and uvrB genes, and to homologs thereof, that have the effect of decreasing the activity of the gene product. Just as the breadth of the claims is great, so is the number of potential mutations that may be made. Not only are there numerous substitutions that may be made, but there are also large numbers of insertions and deletions that may be made in the polynucleotide sequence. Although the number of operative embodiments is also likely to be high, the lack of guidance leading to them tends to show that they are not readily identifiable. Thus, the factors of claim breadth, guidance, and quantity of experimentation tend to favor a finding of undue experimentation. Salmonella, Shigella, M.tuberculosis and Bacillus anthracis are recited in the dependent claims yet the specification fails to show that these bacterium would work in a similar manner. It is unclear of the sequence of the uvrA, uvrB genes in the Salmonella, Shigella and M.tuberculosis and they are extremely different from L.monocytogenes. It is unclear that they would behave in the same manner, e.g., become attenuated in a manner that leads them extremely sensitive to killing yet still maintained their metabolic activity and were able to synthesize and create new protein in response to treatment with psoralen and UVA irradiation. No experimental results are provided for the B.anthracis mutants. B.anthracis is a highly infectious bacterium and it is unclear that the attenuation would result in a non-toxic/lethal bacterium. A sporeless strain is not recited in the instant claims.

The instant fails to demonstrate that any compounds, other than psoralen, would result in an attenuated bacterium which would result in a non-virulent/toxic bacterium which would maintain its metabolic activity and still be able to synthesize and create new protein in a sufficient amount. Experimental results are only shown with respect to psoralen and it would take one of skill in the art undue experimentation to discover and test other nucleic acid targeting compounds and the efficacy of the resultant vaccines.

While those participating in the art of the relevant technology (genetic and protein manipulation) are generally highly skilled, the art is also rife with complexity. See also, discussion above in the written description rejection (demonstrating the lack of obviousness as to what mutations may be operable absent guidance). Knowledge of the sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects that such a mutation would have. See e.g., Bowie, supra. Although Bowie also points out that information gathered from groups of similar or related proteins often helps in making predictions as to the effects of particular mutations. Bowie, pages 1308-1309. However, while the applicant has provided a few related proteins in the specification, there is no discussion as to the structural relationships among them. Rather, the sequences are set out, and it is left to those in the art to run comparisons to determine what the similarities among them are, and to determine which of them are important and which are not. In short, that applicant has invited others in the art to determine what mutations would achieve the desired affect without providing them any guidance indicating what the potential operable embodiments are.

It is the position of the examiner that the novelty of the instantly claimed invention not only lies in the mutation recited in the claims, but the bacterium must be mutated in a certain way in order to attenuate the bacteria in a functional manner, e.g., psoralen and UVA treatment. The specific mutation(s) of the polynucleotide sequence to accomplish decreased biological activity of the encoded polypeptide and the manner of attenuation, is critical to the invention, e.g, not just the phenotype displayed by the mutant bacterium.

Given the complexity of the art, the breadth of the claims, the number of potential mutations in different microbial mutants, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of uvrA and uvrB to target for modifications, in order to produce an attenuated bacterium with the desired phenotype. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification,

reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Bowie et al was also cited for providing evidence that information gathered from groups of similar or related proteins may not be sufficient to show one skilled in the art where to make mutations in a molecule and to have confidence that the mutations will have the desired result (Bowie, pages 1308-1309). Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation.

The claims are also broadly drawn to prevention and treatment of ***any*** disease, with dependent claims including cancer, HIV and hepatitis C prevention. The specification has not enabled any HIV, cancer or hepatitis ***prevention*** methods. There is no know HIV prevention method to date. There is also no know cancer prevention method or vaccine to date. This art area is extremely unpredictable. Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. The state of the prior art is no known prevention methods for these disease, there is extreme unpredictability in treatment and prevention methods

in these infectious disease areas, it would take extreme amounts of guidance and direction and a great quantity of experimentation backed by the presence of working examples to enable this scope of the claims. Accordingly, given the lack of guidance contained in the specification, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicants' Arguments:

Applicants argue that modification with psoralen (S59) and UVA was widely known and effective in inactivating a wide variety of bacteria in the prior art at the time the invention was made. This does not demonstrate prevention or treating a disease as is claimed. The claims are drawn to **a method of treatment or prevention of *any* disease** comprising the use of in some of the claims, soley a modified L.monocytogenes bacterium. Claims 20 and 152 are also vague and confusing because they are drawn to a method of treating or preventing *any* disease in a host yet the claims reads on solely the use of a L.monocytogenes bacterium. It does not appear this bacterium could treat or prevent a disease other than one caused by L.monocytogenes. These claims broadly read on an infinite number of genes, bacterium, diseases, etc. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing

out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Applicants argue that evidence that the *Listeria* which have been treated with the UV-activated psoralen are capable of protecting mice against subsequent challenge with wild-type *Listeria* is provided in the instant specification. This argument has been fully and carefully considered, but is not deemed persuasive since none of the claims are limited to protection against disease caused by *Listeria*. Additionally, the results of efficacy against tumors does not directly correlate to HIV or cancer prevention as encompassed by the broad independent claims and specifically recited in some of the dependent claims.

Claim Rejections - 35 USC § 112-Written Description

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 20, 21, 83-87, 97-107, 109-118, 128-138 and 140-149 and new claims 150-189 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to "A method of preventing or treating ***any*** disease (e.g., the claims include HIV, cancer and hepatitis C prevention) in a host, comprising administering to the host an effective amount of the vaccine of claim 20 a vaccine comprising ***a*** modified L.monocytogenes bacterium, wherein the nucleic acid of the microbe has been modified with psoralen adducts or crosslinks so it is attenuated for proliferation" or "a method of inducing an immune response to an antigen comprising administering to the host an effective amount of a vaccine comprising a modified L.mononcytogenes bacterium, wherein the nucleic acid of the microbe has been modified with psoralen adducts or crosslinks so that it is attenuated for proliferation, and wherein the microbe expresses the antigen." The elected species read on mutations of the uvrA or uvrB genes or both genes, attenuated bacteria comprising such polynucleotides, and species homologs thereof. However, the specification does not provide adequate written description to support methods using any mutation/attenuation resulting in the desired phenotype and attenuation.

There is inadequate written description to support these claims for use in methods of treatment or prevention of any disease.

The specification has only shown an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene (e.g., which attenuates the bacterium's ability to repair itself) which has been attenuated by treatment with psoralen S-59 and ultraviolet

light irradiation wherein the mutant bacterium expresses the heterlologous antigen" with respect to the elected species.

More than a statement of biological function is required to satisfy the 112 1st paragraph written description requirement for a genus of DNA molecules. See e.g. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 U.S.P.Q.2d 1016, 1027 (CAFC 1991); and Fiers v. Revel, 25 U.S.P.Q.2d 1601, 1604-05 (CAFC 1993). In Amgen v. Chugai, the Court of Appeals for the Federal Circuit stated that "[i]t is not sufficient to define [a DNA] solely by its principal biological property, e.g. encoding of human erythropoietin." Id., at 1021. Rather, "what is necessary is that [the applicant] provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims." Id., at 1027. In these statements, the court has expressly stated that a DNA molecule must be described by means of description other than by naming the encoded protein to satisfy the 112 ¶1 written description requirement.

More recently, the Federal Circuit again took this position. In the case University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d 1398, at 1406 (1997), the court stated that defining a cDNA by its function "is only a definition of a useful result rather than a definition of what achieves that result." The court also stated that such a description "does not define any structural features commonly possessed by members of the genus [of claimed cDNAs] that distinguish them from others." Id. Thus, it is clear that identification of polynucleotide by naming the polypeptide it encodes is not sufficient. In the present case, the only description that the applicant has provided for species

homologues of uvrA and uvrB is that they must also encode uvrA and uvrB proteins. Such a description is clearly insufficient to support the claimed genus. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of the uvr gene's coding regions to target for modifications, in order to produce an attenuated bacterium. While it may be obvious to those in the art to make mutations in a gene or protein, to achieve an attenuated bacterium, once the molecule has been identified as necessary for the virulence of the bacterium, it is not immediately obvious to those in the art as to what mutations will be effective. See e.g., Bowie et al., Science 247:1306-1310, page 1306. Bowie et al. presents a discussion on the tolerance of proteins to substitutions in the residue sequence. Although the reference is a discussion of protein substitutions, as the present case is concerned with polynucleotides encoding such proteins, the teachings of the reference are equally applicable to the mutations of the claimed inventions. The reference states first that proteins generally accept a wide variety of substitutions in their residue sequence. However, it also states that some residues may not be substituted at all without loss of the proteins function. The reference also states that the effects of such substitutions are, currently, highly unpredictable. Thus, one skilled in the art would not be able to recognize from the current disclosure any substitutions, or other mutation (except, perhaps, deletion of the whole polynucleotide) that would result in a decreased gene product activity.

As stated above, the Federal Circuit has held that claiming polynucleotides disclosed by their biological function alone is inadequate to meet the written description

and enablement requirements. In the present case, not only does the application claim additional undisclosed polynucleotides without such support, it further claims modifications to both the disclosed and undisclosed polynucleotides by the effect of such modifications.

Applicants are claiming methods of using bacteria and they are claiming said bacteria comprising a mutation in a nucleotide sequence with a specific structure: function relationship in the claims. "The Applicant's are not claiming polynucleotide sequences per se."

It is the position of the examiner that the novelty of the instantly claimed invention not only lies in the coding sequence of uvrA and uvrB polynucleotide sequence, but the bacterium must additionally be mutated in such a way to attenuate the bacteria to desired effect. The polynucleotide sequence, as well as the specific mutation(s) of the polynucleotide sequence to accomplish decreased biological activity of the encoded polypeptide, is critical to the invention, e.g, not just the phenotype displayed by the mutant bacterium.

Response to Applicant's Arguments:

Applicants argue that a variety of genes in a variety of different bacteria genuses had been identified at the time of filing that could serve as targets for attenuating mutations that would attenuate the ability of the bacteria to repair its modified nucleic acid. This argument has been fully and carefully considered but is not commensurate in scope with the claimed invention. There are many genes in a bacterium which if altered or deleted could cause attenuated proliferation and they are not necessarily 'repair genes'.

Applicants focus on uvrA and uvrB mutants, but these are not recited in the bulk of the claims. The claims lack written description for the breadth included in the claims. The specification does not adequately support the breadth of all of the claims that are presented. It cannot be known whether all of the permutations and combinations covered by the claims will be effective for the intended purpose, and the claims are too broad because they may include many inoperative species. Applicants state that they have provided an adequate description and exemplification of their invention as would be understood by persons in the field of the invention. They state that biological properties typically vary, and that their specifications provide for evaluation of the effectiveness of their numerous modified bacterium for treatment or prevention of any disease. It is well recognized that in the "unpredictable" fields of science, it is appropriate to recognize the variability in the science in determining the scope of the coverage to which the inventor is entitled. Such a decision usually focuses on the exemplification in the specification. See, e.g., Enzo Biochem, 296 F.3d at 1327-28 (remanding for district court to determine "[w]hether the disclosure provided by the three deposits in this case, coupled with the skill of the art, describes the genera of claims 1-3 and 5"); Lilly, 119 F.3d at 1569 (genus not described where "a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus" had not been provided); In re Gostelli, 872 F.2d 1008, 1012 (Fed. Cir. 1989) (two chemical compounds were insufficient description of subgenus); In re Smith, 458 F.2d 1389, 1394-95 (CCPA 1972) (disclosure of genus and one species was not sufficient

description of intermediate subgenus); In re Grimme, 274 F.2d 949, 952 (CCPA 1960) (disclosure of single example and statement of scope sufficient disclosure of subgenus).

Status of claims

8. The claims are **not** provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 39 and 40 of copending Application No. **10/773,792** because the claims are drawn to mutants with completely different mutations. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. *However, this rejection may apply if amendments are made to the claims of either application*.

The claims are also not rejected under double-patenting with respect to co-pending application **10/883,599** because that application no longer recites any method claims. If that application rejoins any method claims, a double-patenting rejection may be necessitated because the compositions read on the compositions used in the claimed methods.

9. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

10/7/08